REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

By the foregoing amendment, claims 4 and 6 have been amended to correct certain typographical errors and place the claims in better form for United States practice. Additionally, new claim 20 has been added. Support for this claim can be found throughout the originally filed application, including for instance, on page 12, lines 2-4, of the specification. Thus, no new matter has been added.

Before addressing the Office Action, a brief discussion of applicants' invention is believed to be in order. Prior to applicants' invention, "a drug delivery system [was] desired that circulates stably having no interaction with protein or cells in blood flow and has increased interaction with cells only in a diseased site so that it can deliver the drug to the cells." SPECIFICATION at 4. Applicants have discovered "a liposome that exhibits target directive capability for a drug, DNA, peptide and protein by a change in pH at a diseased state." SPECIFICATION at 5. The liposome of the present invention contains specified amounts of a basic compound and an acidic compound and, in consequence, is electrically neutral under physiological pH conditions while cationic under acidic conditions. *See* CLAIMS.

At a physiological pH (of ca. 7.2 to 7.6), the above basic and acidic compounds are each ionized at a predetermined ratio so that the liposome is electrically neutral and does not interact with a substance of negative charge of a cell, a protein, and so forth. At a pH (of ca. 5 to 7) which is on the acidic side of the physiological pH range, on the other hand, the ionization of the acidic compound is

suppressed and the liposome becomes cationic and interacts with the substance of negative charge.

Therefore, the liposome of the present invention interacts with a substance of negative charge at the target site where the pH is decreased, such as an inflammatory site and a tumor site, whereby its affinity for cells is improved and the liposome is efficiently localized (namely, accumulated) on the target site, with its localization outside the target site being prevented.

Turning now to the Office Action, the Examiner has maintained the following rejections under 35 U.S.C. § 103(a):

(i) Claims 1, 4-5, 7 and 10-18 under 35 U.S.C. § 103(a) as allegedly being unpatentable over EP 0 636 363 ("EP '363");

(ii) Claims 1-5, 7 and 10-18 have been rejected under 35 U.S.C. § 103(a) as purportedly being unpatentable over JP 09 263579 ("JP '579");

(iii) Claims 8-9 have been rejected under 35 U.S.C. § 103(a) as purportedly being unpatentable over EP '363 or JP '579 further in view of Gold (U.S. Patent No. 6,465,188); and

(iv) Claims 6 and 12 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over EP '363 in combination with either Schneider (U.S. Patent No. 6,258,378) or Malone (PNAS, 86:6077-81 (1989)).

Each of these rejections is respectfully traversed.

In proceedings before the United States Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. The Examiner can satisfy this burden only by showing some

objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to modify or combine the relevant teachings of the references. The patent applicant may then attack the Examiner's *prima facie* determination as improperly made out, or the applicant may present objective evidence tending to support a conclusion of nonobviousness. *See In re Fritch*, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992).

Here the Examiner's *prima facie* case of obviousness is improperly made out because none of the cited references teach or suggest the molar ratio of the basic or acidic compounds based on the total liposome membrane constituents. Moreover, contrary to the Examiner's allegation, there is no motivation to modify the amount of any basic or acidic compounds in the liposomes of the cited art to arrive at the amount claimed in the present application. Additionally, applicants have provided objective evidence (set forth in the Specification and discussed further below) to support a conclusion of nonobviousness.

I. EP '363, ALONE OR IN COMBINATION, FAILS TO RENDER THE CLAIMED INVENTION UNPATENTABLE

EP '363 describes a liposome and use of a compound containing an aliphatic primary or secondary amino group, amidino group, or aromatic primary or secondary amino group in the liposome. Phosphatidic acid is mentioned as an example of phospholipid and glucuronic acid and silaic acid as examples of the surface modifying agent.

However, EP '363 does not teach an embodiment or example in which a specified amount of a basic compound such as an aliphatic primary or secondary amino group, amidino group, or aromatic primary or secondary amino group is used

in combination with a specified amount of phosphatidic acid, glucuronic acid. Nor is there any suggestion of such an embodiment.

The liposome described in EP '363 has a high affinity for cells because such a basic compound as the compound containing an aliphatic primary or secondary amino group, amidino group, or aromatic primary or secondary amino group interacts with a substance of negative charge of a cell, a protein, and so forth. This is true whether the pH is within the physiological pH range or on the acidic side of the range. In other words, the liposome of EP '363 is localized not only on the inflammatory site or tumor site where the pH is on the acidic side of the physiological pH range but also any site with no abnormalities due to the fact that cells are of negatively-charged substance.

It is described in EP '363 that the liposome is selectively accumulated on an injured portion of vascular endothelium. Such a description, however, does not mean that a larger amount of the liposome of EP '363 is localized on an injured portion of vascular endothelium as compared with other portions, but means that the liposome of EP '363 is localized on an injured portion of vascular endothelium in a larger amount than the liposome comprising no basic compounds. Therefore, contrary to the Examiner's assertion, there is no motivation to modify the amount or molar ratio of the acidic and basic compounds of the liposome to arrive at applicants' claimed liposome which exhibits the target directive capability by a change in pH.

The Examiner has also argued that "EP does not teach specifically chondroitin sulfate as the glycosamincglycan. However, in view of [EP's] teachings of the use any glycosaminoglycans, one of ordinary skill in the art would have been motivated to use any glycosaminoglycan with a reasonable expectation of success".

It is noted, with regard to claim 17, that chondroitin sulfate C is recited neither as a constituent of the liposome nor as a drug incorporated in the liposome. Chondroitin sulfate, as one of glycosaminoglycans occurring on the cell membrane, in the extracellular matrix, and so forth, is produced by many types of cells and may be expressed in accordance with the malignancy of a cancer in certain cancer cells. In the present invention, chondroitin sulfate is used as a putative target of the liposome having the target directive capability.

Neither the Gold patent, the Schneider patent nor the Malone reference remedy any of the serious deficiencies discussed above with regard to EP '363.

Since EP '363, whether taken alone or in combination with the Gold patent, the Schneider patent or the Malone reference, fails to teach or suggest applicants' claimed invention, withdrawal of rejections (ii), (iii) and (iv) above, are respectfully requested.

II. JP '579, ALONE OR IN COMBINATION, FAILS TO RENDER THE CLAIMED INVENTION UNPATENTABLE

JP '579 describes a liposome and use of a piperidine derivative in the liposome. Phosphatidic acid is mentioned as an example of phospholipid and glucuronic acid and, silaic acid as examples of the surface modifying agent.

However, JP '579 does not teach an embodiment or example in which a basic compound such as a piperidine derivate is used in combination with a specified amount of phosphatidic acid, glucuronic acid, or silaic acid. Nor is there any suggestion of such an embodiment.

The liposome described in JP '579 has a high affinity for cells because such a basic compound as the piperidine derivative interacts with a substance of negative charge of a cell, a protein, and so forth. This is true whether the pH is within the

physiological pH range or on the acidic side of the range. In other words, the liposome of JP '579 is localized not only on the inflammatory site or tumor site where the pH is on the acidic side of the physiological pH range but also any site with no abnormalities due to the fact that cells are of negatively-charged substance. Therefore, contrary to the Examiner's assertion, there is no motivation to modify the amount or molar ratio of the acidic and basic compounds of the liposome to arrive at applicants' claimed liposome which exhibits the target directive capability by a change in pH.

The Examiner has also argued that "JP does not teach specifically chondroitin sulfate as the glycosamincglycan. However, in view of [JP's] teachings of the use any glycosaminoglycans, one of ordinary skill in the art would have been motivated to use any glycosaminoglycan with a reasonable expectation of success". It is noted, with regard to claim 17, that chondroitin sulfate C is recited neither as a constituent of the liposome nor as a drug incorporated in the liposome. Chondroitin sulfate, as one of glycosaminoglycans occurring on the cell membrane, in the extracellular matrix, and so forth, is produced by many types of cells and may be expressed in accordance with the malignancy of a cancer in certain cancer cells. In the present invention, chondroitin sulfate is used as a putative target of the liposome having the target directive capability.

Neither the Gold patent, the Schneider patent nor the Malone reference remedy any of the serious deficiencies discussed above with regard to JP '579.

Since JP '579, whether taken alone or in combination with the Gold patent, the Schneider patent or the Malone reference, fails to teach or suggest applicants'

claimed invention, withdrawal of rejections (ii) and (iii) above, are respectfully requested.

III. RESPONSE TO THE EXAMINER'S ARGUMENTS ON PAGES 4-5 OF THE OFFICE ACTION REGARDING THE UNEXPECTED RESULTS OF THE CLAIMED INVENTION

A. Figures 3 and 4

Applicants previously indicated that Figure 4 shows unexpected results. In response, the Examiner indicated that "a careful evaluation of data in Figures 3 and 4 [shows] that the composition in comparative example actually accumulates in higher amounts either at pH 5.5 or 7.4 than the composition in example 9."

The data in Figures 3 and 4 show the amounts of the liposomes bound to proteoglycan and cells, respectively. The liposome of Comparative Example 7 is bound to both of the proteoglycan and the cells indeed in a larger amount than the liposome of Example 9, whether at pH 6.5 or pH 7.4.

In both of the cases of proteoglycan and cells, however, the amount of the liposome of Comparative Example 7 bound at pH 6.5 is almost the same as that at pH 7.4. Therefore, when actually administered in the blood, the liposome of Comparative Example 7 is bound not only to the inflammatory site or tumor site where the pH is on the acidic side of the physiological pH range but also any site with no abnormalities. In other words, the liposome is in no way specifically bound to the target site such as an inflammatory site or a tumor site. The liposome of Comparative Example 7 may be bound to a site with no abnormalities before reaching the target site, an efficient localization on the target site being thus inhibited.

In contrast, the amount of the liposome of Example 9 bound at pH 6.5 is significantly larger than that at pH 7.4. Therefore, when actually administered in the blood, the liposome of Example 9 is chiefly bound to the inflammatory site or tumor site where the pH is on the acidic side of the physiological pH range and almost not to a site with no abnormalities. That is to say, the liposome is specifically bound to the target site such as an inflammatory site and a tumor site. The liposome of Example 9 can reach the target site without being bound to a site with no abnormalities so that it is localized on the target site efficiently.

Although the liposome of Comparative Example 7 is bound to both of the proteoglycan and the cells at pH 6.5 in a larger amount than the liposome of Example 9 as shown in Figures 3 and 4, the former is thus inferior to the latter in the rate of localization on the target site when actually administered in the blood.

The comparison between Example 9 and Comparative Example 7 as above also applies to the comparison between the liposome of the present invention and the liposome disclosed in EP '363 or JP '579. The liposomes described in EP '363 (particularly in the Examples) and JP '363 (particularly in the Examples each have a lower rate of localization on the target site when actually administered in the blood, as compared with the liposome of the present invention.

The Examiner has argued with respect to the Examples that "there is no statistical evaluation of the data". Examples of the present invention, however, are highly reproducible because they were carried out *in vitro*. Accordingly, it is not necessary to statistically evaluate a large amount of data, which may be required in *in vivo* experiments.

The Examiner has also argued with respect to the Examples that "instant claimed range of pH values is 5 to 7 and there are no comparative values for pH 5 and 7 (instant lower and upper limits)."

In the Examples, however, the effects of the present invention have been shown at pH 6.0 and pH 6.5 and, moreover, the acidic compounds used were each a phosphoric acid monoester derivative or a compound having a carboxyl group or its salt so that it was chemically expected that the ionization of the compounds was suppressed at a pH of ca. 5 to 7 and the compounds contributed to the effects of the present invention.

It is indicated by the upper limit of the pH set to 7 that the liposome of the present invention is seldom bound to a site with a normal pH in the living body (physiological pH), which is generally ca. 7.4, but bound to an inflammatory site or tumor site with a smaller pH.

The lower limit of the pH is set to 5 because a site with a pH smaller than 5 is generally not present in the living body (except for the stomach) and. because it is desired that such liposomes as are hound not to a site of pH 5 but to a site of pH 4, if any, he excluded from the scope of the present claims. If the liposome prepared in Example, for instance, 6 or 3 is bound to a site of pH 4, it is not included in the scope of the present claims.

B. Claim Scope

The Examiner has also argued that the "instant claims are so broad with respect to the generic term, 'basic compound' and 'acidic compound' and applicant has not shown any unexpected results using compounds falling within these broad terms".

As for the "basic compound," unexpected results have been demonstrated using three specific compounds, namely, 3, 5-dipentadecyloxyhenzarnidine hydrochloride (Examples 1 to 4), l,2-dipalmitoyl-3- trimethylammoniumpropane (Examples 5 and 6), and 1,2-dipalmitoyl-3-dimethylammoniumpropane (Examples 7 and 8). As stated above, one of the important aspects to the effects of the present invention is that the basic compound used exhibits a cationic character. Any basic compound may be quite likely to contribute to the effects of the present invention as long as it exhibits a cationic character and, in view of this, the generic term "basic compound" cannot be considered as unduly broad.

The "acidic compound" is limited in claim 1 to "a phosphoric acid monoester derivative, or a compound having a carboxyl group or its salt". Also in the Examples, unexpected results have been demonstrated using five specific compounds, namely, myristic acid (Examples 1, 5 and 6), phosphatydic acid (Examples 2 and 9), sodium prednisolone phosphate (Example 3), sodium riboflavin phosphate (Example 4), and palmitic acid (Examples 7 and 8). As stated above, it is another point which is important to the effects of the present invention that the acidic compound used has a characteristic that, at a physiological pH, it is ionized at a predetermined ratio and its ionization is suppressed at a pH which is on the acidic side of the physiological pH range. Any acidic compound, as a phosphoric acid monoester derivative or a compound having a carboxyl group or its salt, may be quite likely to contribute to the effects of the present invention as long as it has the above characteristic and, in view of this, the generic term "acidic compound" cannot be considered as unduly broad.

Finally, the Examiner has alleged that "the data in the examples are not commensurate with the scope of the claims with respect to the basic compound,

acidic compound and the mole percentages." In Example 1, however, the amount of the basic compound was 7.3 mol% and that of the acidic compound 3.7 mol%, each being within the scope of claim 1. The situations are the same in Examples 2 to 9.

IV. CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited

In the event that there are any questions relating to this Amendment and Reply, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Date: February 28, 2005

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